



Letter

Neonatal B-cell suppression after in utero exposure to R-CHOP

Rituximab is a monoclonal antibody directed against the CD20 antigen on B-lymphocytes. It is an approved therapy either as a single agent or in combination with other drugs for non-Hodgkin's lymphoma and chronic lymphocytic leukemia. It has also been used in autoimmune disease states such as systemic lupus erythematosus and idiopathic thrombocytopenic purpura.

Rituximab therapy, which results in B-cell depletion, is commonly associated with an increased risk of infection in those patients given this medication.¹ This risk is also incurred “by proxy” when rituximab is administered to women during pregnancy and may deplete B lymphocytes in the newborn. A review of the literature shows that the vast majority of children exposed to rituximab in utero clinically did very well in the immediate postpartum period. More specifically, of the 153 known outcomes of cases of rituximab administration during pregnancy, most resulted in live births (60%). Notably, of these cases, 21% resulted in first-trimester miscarriage and 18% in elective abortions.²

Six case reports have described rituximab use with combination therapy for hematologic malignancy. Of these 6 cases, 2 had documented B-cell depletion at birth but normal values by 18 weeks of age. Six cases have been published concerning rituximab use in nonmalignant hematological disorders, and 5 of these cases described initial hematologic abnormalities, including 2 patients with B-cell depletion at birth, both of which normalized by 6 months of age. Further, one of these patients was noted to have low IgM, IgG, and IgA at birth. No follow-up data were available on the third patient, but clinically the patient was asymptomatic at 1 year follow-up. Two cases have been published of rituximab use in patients with rheumatoid arthritis. There were no abnormalities noted at birth in these patients. Lastly, 7 case reports have been published discussing rituximab use, pregnancy, and autoimmune diseases. These case reports reviewed data on a total of 11 patients. One child was born premature and died shortly after birth of undocumented causes. No hematologic abnormalities were noted in any of these

children exposed to rituximab in utero^{2–5} (Genetech Medical Letter, email communication, April 29, 2013).

We describe a case of a 30-day-old boy who was referred to our clinic for abnormal laboratory values in the setting of in utero exposure to maternal chemotherapy. The patient was born to a 28-year-old gravida 1/para 1. The mother was blood type O negative with normal prenatal laboratory test results. The pregnancy was complicated by maternal diagnosis of non-Hodgkin's lymphoma at 29 weeks estimated gestational age. For treatment of the malignancy, the mother received 3 rounds of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) therapy at 8, 5, and 2 weeks before delivery.

In spite of the pregnancy complications, the patient was born vigorous at 38 5/7 estimated gestational age. Since birth, the child had been growing and feeding well, with a 2-pound weight gain and no episodes of diarrhea, fever, thrush, or systemic infections.

On our initial evaluation, the patient had a completely normal physical examination. The patient had a normal white blood cell count, hemoglobin, and platelet count, with an absolute neutrophil count of 1,040 cells/ μ L and a low absolute lymphocyte count of 1,300 cells/ μ L. His immunoglobulin (Ig) G was 349, but his IgM/IgA levels were zero. Furthermore, the patient had no detectable CD19 cells in spite of normal numbers of T cells and natural killer cells (Table 1).⁶ Because the patient was progressing well, no intervention was recommended, and the patient was seen 1 month later.

At the patient's 2-month visit, the absolute neutrophil count was not obtained, but the patient was noted to have an IgG level of 166 and continued absence of CD19, IgA, and IgM cells (Table 1).⁶ Shortly after the 2-month visit, per parental preference, patient was only given the Pneumococcal 13-valent conjugate vaccine. He had no adverse reaction to this immunization and is currently receiving his routine vaccines on a delayed scheduled. Of note, he was never given rotavirus vaccine. After his 2-month visit, he continued to be asymptomatic, with no fevers, infections, or developmental problems. His 6-month laboratory tests were

Table 1
Laboratory values on days 1, 30, 60, and 180

Lab	Birth	Day 30	Day 60	Day 180
CD 19	N/A	0	0	1.76 (0.61–2.6)
IgM (mg/dL)	N/A	0	0	27 (33–102)
IgA (mg/dL)	N/A	0	0	10 (8.1–68)
IgG (mg/dL)	565 (636–1,606)	352 (251–906)	166 (206–601)	211 (215–704)
CD3 (abs ct $\times 10^9/L$)	N/A	3.0 (2.3–7.0)	3.3 (2.3–6.5)	3.3 (1.9–5.9)
CD4 (abs ct $\times 10^9/L$)	N/A	1.88 (0.4–3.5)	2.2 (1.5–5.0)	2.18 (1.4–4.3)
CD8 (abs ct $\times 10^9/L$)	N/A	1.2 (0.2–1.9)	1.2 (0.5–1.6)	1.12 (0.5–1.7)
CD 56 (CMM)	N/A	97 (23–797)	71 (23–797)	107 (23–797)

Abbreviation: Ig, immunoglobulin.

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drawn and showed normalization of IgG, IgM, IgA, and CD 19 (Table 1). Twelve-month immunological laboratory tests were ordered to further assess immune function, to evaluate possible residual effects of rituximab exposure, and to evaluate immune status before administration of routine 12-month live virus vaccines. Unfortunately, however, the patient has been lost to follow-up.

Although supplemental immunoglobulin may be necessary in some cases of newborns exposed to rituximab in utero, this case further suggests that the risk of infection resulting from maternal rituximab-induced depletion of B cells in the newborn may not be significantly increased and that in an otherwise healthy infant, conservative, prospective management of this secondary B cell deficiency may be appropriate.

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